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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,632	06/09/2000	Susan Lindquist	27373/34978A	2820
7590	06/26/2006			EXAMINER TURNER, SHARON L
Marshall O'Toole Gerstein Murray & Borun 6300 Sears Tower 233 South Wacker Drive Chicago, IL 60606-6402			ART UNIT 1649	PAPER NUMBER
DATE MAILED: 06/26/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/591,632	LINDQUIST ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 23 March 2006.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 65,81,101,103-110,117,118,121-135,137-140 and 143-162 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 121-135,137-140, 144-145, 150-155, 157-161 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) 65,81,101, 103-110,117-118, 121-135, 137-140 and 143-162 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 65,67,81,101-110,116-119,124-138,140-143 and 145-149.

Response to Amendment

1. The amendment filed 12-5-05 has been entered into the record and has been fully considered. The sequence revisions of 2-2-06 and 3-23-06 are accepted and place the case in compliance with the sequence rules.
2. Claims 67, 81, 101, 103-110, 117-118, 121-135, 137-140, and 143-162 are pending as revised 12-5-05.
3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.
4. As a result of Applicants amendment, all rejections not reiterated herein have been withdrawn.

Election/Restrictions

5. Applicant's election with traverse of Group VII, claims 121-123, 139 and 144 and peptide of SEQ ID NO:2, particularly residues of NM regions (1-253), N region (1-123) and substitution of cysteine residue in the reply filed on 5-9-05 is acknowledged. The traversal is on the ground(s) that there is no substantial burden (pp. 12-13 of response), no search burden with respect to SEQ ID NO:2 and substitutions (pp. 13-14), that there was a failure to identify characteristics that define the restriction groups (p. 14), that the restriction of fiber/polymer claims was improper (pp. 14-15), that the restriction of polypeptides was improper (p. 15-16) and that the restriction to delineate the molecular embodiments is improper (p. 16-17). This is not found persuasive because the search burden with respect to each of the newly delineated products is substantial. The delineated products were newly amended as presented in the 7-19-04 submission,

thereby necessitating the 2-7-05 restriction. These claims were not previously searched and or considered on the merits by the previous Examiner during the course of examination. In contrast to Applicant's assertion, the record is clear that the previous search and examination based upon previous restriction was limited to the extent of SEQ ID NO:2 and cysteine substitutions, see action of 1-13-04, page 2, third paragraph.

The newly recited products are patentably distinct and distinguished as separately claimed. They differ in amino acid composition and in higher order structures as set forth in several independent and dependent claims drawn to various forms of "filamentous polymers", "fibrous polymers", "fibers", and distinct "polypeptides". The prosecution history is noted. However, no claims are instantly deemed to be allowable. Moreover, as set forth in the restriction requirement, the restriction was instituted in part upon Applicants assertion of patentability of particular higher order structures. Applicants reference to a SCHAG amino acid sequence is noted. However, as delineated in the specification, the SCHAG amino acid sequence is variable in amino acid sequence and in higher order structures that may be formed. It is common practice within the PTO that polypeptide sequences may be restricted one from another as they each comprise different non-coextensive searches. It is not clear that any polypeptides share each of the higher order composites as separately claimed. The claims remain drawn to separate non-coextensive generic or sub-generic recitations and the relationships amongst the different sets are not set forth.

Neither have Applicants stated that the different claim sets are not patentably distinct, nor is it clear that a reference to any one structure would constitute a reference

to any other. Restriction is therefore maintained until evidence of allowability or admission on the part of Applicants that the claims are not patentably distinct in which case a reference to one species may be suitably used against another. The Examiner does further note different classification of higher order product structures, specifically to various polymers, fibers, and filaments, further evidencing the basis for restriction. To the extent that the products are not evidenced to be the "same", restriction therefore is maintained. It is further noted that previous arguments on the record with respect to cited art indicate Applicants belief that particular higher ordered peptide structures are patentable over the same products which are in different aggregate "form". Indeed the previous Examiner removed prior art rejections upon such argument by Applicants. Accordingly, restriction is maintained until the indication of allowable subject matter or until resolution over the issue of patentable "distinctness" amongst the various structural compositions. It is noted that the elected invention as delineated includes recitations to "polypeptides" and to "fibrous polymers" and are examined to the extent distinguished via the claims. Resolution of these issues and "finality" of the restriction requirement is deferred until such time that the Examiner has reviewed Applicant's response to the instant Office Action. The requirement is still deemed proper and is therefore maintained.

In the response of 12-5-05 Applicant's argue the restriction requirement as set forth at pp. 18-22. This traversal is only partially persuasive as set forth below. The withdrawn claims are maintained as restricted but are placed into a single group. The examined claims are as noted below. Applicant's argue that the generic claims in the

instant office action have improperly been withdrawn and that they encompass the elected subject matter. In contrast to this argument, the Examiner notes that the only withdrawn claims are to those of higher order structure that are not generic to, linked or dependent upon the elected polypeptides. Instead the structural constraints are different. The instantly elected subject matter is that of polypeptides. It is noted that the previous action was prepared with respect to claims 139-140 that recite higher order structure (fibrous polymers). These claims were included because of their dependency from elected polypeptide claims. The Examiner did set forth a full basis for restriction. Applicant's now make clear that, "The Examiner is correct that a distinction has been made between aggregates that are not higher ordered aggregates... and polymers/fibers/filaments that are ordered aggregates." It is clear that the invention of these higher order structures are asserted to be of a patentably distinct nature from that of polypeptides which is the elected invention. Accordingly, the claims to which Applicant refers are not deemed as generic but a different invention as distinguished via different structure. Applicant's are also referred to a basis for restriction via different classification. In particular, Applicants argue that these higher order structures are directed to nanotechnology solutions, see Remarks, p. 16. The class definition of class 977, Nanotechnology makes it clear that these structures are separable, but with respect to the basic elements where no complex structure is evidenced, the basic elements are classified based upon their molecular structure. Again as set forth, such distinction allows for restriction between the elected peptides and the higher order structures.

Applicants request for their higher ordered structures to be examined consistent with the art directed to such nanotechnology applications and secondary structure consistent with prions. As Applicant's point out, this is an invention assigned to a different art unit. As such, restriction should be maintained so that those claims may be properly pursued within an art unit that normally examines that subject matter. However, to the extent that no structural distinction is made beyond the elected polypeptides, this subject matter should properly stay within a polypeptide art unit and be examined as such.

Applicants point out that substitution at position 2 of SEQ ID NO:2 was improperly withdrawn. In response, it is unclear to exactly which claims Applicant's are referring. However, to the extent that Applicant's are referring to claim 145, this argument is persuasive. It is noted that the Examiner, in error, examined substitution at residue 184 instead of residue 2. Claim 144 will continue to be considered herein.

Claims 124 and dependent claims were previously withdrawn as they are directed to a separate unsupported fragment (2-113 and 2-253) than that elected (1-123 and 1-253 note election). However, Applicants continue to pursue such subject matter as presented in new claims 150-155. As the sequences only differ in few residues, the Examiner will now examine these claims. However, no further sequence variation will be tolerated. Applicants may wish to review the subject matter to verify that the claims are drawn to the particular fragments desired as residues 2-113 vs. 2-123 may be a typographical error. Inclusion of newly presented SEQ ID NO:10 is non-elected and search and examination thereto is not extended.

The Examiner points out that the search was extended beyond the single SEQ ID of SEQ ID NO:2 only to the extent of the elected fragments (SEQ ID NO:2, residues 2-113 and 2-253), cysteine substitutions at residue 184 (not applicable to fragments) and now residue 2 will be considered. Applicants argue no search burden and assert that the previous Examiner's inclusion of other claims in previous actions evidences such. However, the claims are separable and patentably distinct. Moreover, the subject matter is divergent and as Applicant's continue to argue a peptide may not necessarily approximate the higher ordered structures. Examination of the multiple inventions in a single application would bear substantial burden on the part of the Examiner, particularly as argued by Applicant's, the subject matter is outside of the subject matter within the instant art unit. In contrast to the analysis by the previous Examiner, the record now makes clear that particular claims are to polypeptides and particular claims are directed to particular higher ordered aggregates which are deemed to be patentably distinct, and do not share similar search. For example a sequence search may not necessarily reveal art to such higher ordered aggregates and vice versa. Accordingly, there is substantial search burden on the Examiner. The prosecution history is not inclusive of the entire current claim set as the claims have been significantly amended during prosecution, necessitating new restriction and introducing new issues, new search and examination requirements. Further in contrast to Applicants assertion that there is no search burden to substitutions within SEQ ID NO:2, the Examiner notes that substitution at any one or more amino acid positions may constitute separate search and are burdensome to the PTO and it's search systems as they each require separate

search. Claims 117 and 118 are substantially amended as set forth and accordingly any previous indication of allowable subject matter is irrelevant to instant claims in view of the substantial rejections of record set forth herein.

Applicant's comments at subparagraph D are noted. However Applicants need only look at the separately recited claim limitations to the different structural and functional requirements of the separately restricted groups. It is further noted that the separate limitations may be separately classified. The Examiner would only consider rejoinder upon evidence of allowable and linking claim sets. Rejoinder of the higher ordered structures would be under the purview of an Examiner familiar with examination of those structures. Applicants have previously and continually asserted that the higher order structures are not the same. The recitations of the claims distinguish different structural and functional requirements. Accordingly, restriction is deemed proper. If the structures are not patentably distinct, Applicants may specify so and/or indicate where the structures are the same and inseparable. It is commonplace for the PTO to separate different sequences, different fragments of sequences, and even single amino acid substitutions amongst a singular sequence. This is because such single amino acid substitutions or differences in sequence structure or length are commonly recognized as patentably distinct in the art. Accordingly, the restriction requirement as set forth is proper. It is noted that the Examiner has already allowed substantial variability in search and substantial burden via the consideration of numerous substitutions amongst the full length of SEQ IDN O:2 and even in two separately recited fragments, specifically 2-113 and 2-253. The restriction is proper and no further

substantial search burden can be considered herein. Rejoinder would only be considered upon the indication of allowable subject matter, properly linked claims and compliance with all statutes. Claims to higher order structures will only be addressed where dependent upon claims directed to elected polypeptides. In this way prosecution should establish whether the peptides are free of the prior art and/or whether the higher order structures are an inherent or intrinsic property of any prior art molecule.

Claims 67, 81, 101, 103-110, 117-118, 121-135, 137-140, and 143-162 are pending as revised 12-5-05.

Claims 67, 81, 101, 103-110, 117-118, 143,146-149, 156 and 162 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. These claims are directed only to higher ordered structures and the structures also vary substantially in amino acid composition as recited in comparison to the elected polypeptides. The claims are not written generically to the elected polypeptide claims. Accordingly, restriction of these claims is proper and is therefore made Final. As originally set forth the claims are separably classifiable. Applicants additionally note that the higher ordered structures are related to nanotechnology and as such are classifiable in class 977.

Claims 121-135, 137-140, 144-145, 150-155, 157-161 are now under examination.

Claim Objections

6. Claim 144 is objected to because of the following informalities: The claims recites a substituted amino acid selected from "glutamate" and "aspartate". The art

standard term for these amino acids is generally Glutamic Acid and Aspartic Acid, abbreviated in the literature as "Glu", or "E" and "Asp" or "D" in reference to amino acid sequences.

In the 12-5-05 response Applicants agree that these are equivalent terms but prefer to not amend based upon the original language of the specification.

This argument is considered persuasive. The record notes that the terms are equivalents.

7. Claims 150-155, 157-161 to the extent of elements (d)-(f) are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as the basis for another multiple dependent claim. In this case it is not the full claims that are multiple dependent but simply elements (d)-(f). See MPEP § 608.01(n). Accordingly, the scope of these elements is indeterminate and nearly unsearchable. These recitations are objected to and the structural limitations intended should be clarified.

Priority

8. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 121-123, 139-140 and 144 of this application. The claims differ substantially from that disclosed within the provisional and originally filed specification. In particular the peptides of claims 121-123 and 144 differ in composition and further the "fibrous polymer" newly recited is not apparently disclosed. Accordingly, the effective filing date awarded for the purposes of examination is that of instant filing date 6-9-00. Traversal should delineate where support may be found for instant recitations within the specification as originally filed and within the provisional.

Applicants argue in the 12-5-05 response that allegations with respect to priority should be stricken absent ex parte examination with an intervening reference bearing on patentability and note to MPEP 201.15. No comments with respect to the correctness of the rejection or specific support for the noted elements is provided with the exception of the comments with respect to traversal of the new matter rejection. Accordingly, the lack of a finding for support remains and the case is examined with respect to benefit of the later filing date of 6-9-00. Prior art is cited as noted.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 121-135, 137-140, 144-145, 150-155 and 157-161 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The claims as amended differ substantially from those originally filed. Moreover, the claims newly delineate a "fibrous polymer" which recitations are not apparently supported as claimed. Support for the recitations of the claims should be provided from the specification as originally filed.

Applicants point to support as noted particularly at pp. 23-24 of the 12-5-05 response Section VI, subparagraph A with reference to pp. 6, 8-11, 20, 23-25, 27-31, Examples 9-10. Applicant's arguments filed 12-5-05 have been fully considered but are not persuasive. None of the noted passages serves to define, clarify or provide direct support for any composition as recited. In particular, Applicants should review the scope of the claims as directed to "comprising a fragment thereof...". Rejection therefore is maintained.

Moreover as to the newly recited claims, support is not found for these recitations. In particular,

11. Claims 121-135, 137-140, 144-145, 150-155 and 157-161 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes various polypeptide sequences consisting of Sup35 and Ure2 amongst specific chimeric constructs for example which are disclosed as capable of aggregating as analyzed via spectroscopy or electron micrographs, see for example pp. 44-92. The specification also refers to a "SCHAG amino acid sequence" inclusive of a nearly unlimited number of multiple different amino acid compositions and various aggregate structures as contemplated throughout pp. 6-12 of the specification. The claims as written recite various polypeptides, polypeptide fragments and higher order structures of "fibrous polymers" comprising fragments of substituted amino acids that "self-coalesce" into "higher order aggregates". These recitations encompass various fragments, portions and aggregates that are of nearly unlimited structural breadth. Yet, the specification is limited to experimentation with only particular Sup35/URE2 variants and analysis via spectroscopy and electron micrographs. The instant disclosure of particular polypeptides analyzed for second order characteristics via binding or aggregation with spectroscopy or EM, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc.,

107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”) Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, “requires a precise definition, such as by structure, formula, chemical name, or physical properties,” not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, “an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself.” Id at 1170, 25 USPQ2d at 1606.”

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification however, fails to delineate the structural constraints of a “fibrous polymer” and fails to distinguish those amino acids and conditions required to form them. Further, the specification fails to delineate the structural constraints and conditions whereby various different aggregate structures may be formed. Protein aggregation is dependent upon multiple conditions inclusive of the amino acid sequence of the peptides, pH, temperature, salt concentration, the presence of alternative peptides, cell membranes and other

components that are of nearly unlimited breadth. Such is extensively exemplified throughout the IDS. For example, IDS C12 Dagkesamanskaia teaches differential effect of fusion of glutathione S-transferase on aggregation of yeast Sup35 protein. IDS C15 DePace notes critical roles for amino-terminal Glutamine/Asparagine repeats in yeast prion aggregation. IDS C56 Glover notes the ability of various Hsp proteins to abrogate aggregation. IDS C64 Jackson notes various conditions (oxidation/reduction etc) that affect prion (aggregate) formation. Accordingly, the description provided is insufficient to teach the conditions and structural constraints required whereby suitable "fibrous polymers" and/or "higher ordered aggregates" may be formed.

Applicants argue in the 12-5-05 response that the specification provides putative SCHAG proteins at p. 7, that the application contemplates SCHAG genera and provide guidance to structure-function predictions and fiber forming properties as disclosed at pp. 8-9, 11, 54-58, Example 3, 5, 8, and 9, part B.

These arguments have been fully considered but are not persuasive. The scope of the claims is nearly inclusive of any polypeptide and nearly any polypeptide has higher order structure, may bind and/or aggregate. The conformation of nearly any peptide further depends upon particular environmental conditions. While the specification does teach particular peptides and particular staining with congo red or EM measurement, such does not allow the artisan to predict which structures will conform to the claimed conformations under any particular conditions. The ability of making and testing is not a description of those sequences that actually conform. A putative list of peptides does not provide for clarification of which members actually fall within the

genus. Similarly, such a list does not clarify the conditions under which those peptides may adopt the asserted secondary and tertiary structure. Most importantly there is no correspondence or link between the claimed structures and the provision of the asserted structure which is not defined over any amino acid sequence. Accordingly, adequate written description is not found.

Moreover, to the newly recited claims and polypeptide claims previously withdrawn, the Examiner notes that new claims 150-155 and 157-161 are only directed to polypeptides in the absence of any functional recitation or referral to secondary or tertiary structure such as for example “a polymer”, with “fiber morphology”, “fibrous polymer”, that “self-coalesce”, or that form “higher ordered aggregates”. Moreover, the specification does not specifically define any of these terms. In contrast the specification throughout pp. 6-12 refers to any number of variable associations that may be so qualified or excluded. Claim 130 recites, “wherein the polypeptides has substantially the same fiber forming properties as a polypeptide comprising amino acids 2-253 of SEQ ID NO:2 as assessed by electron microscopy of polypeptide aggregates, to assess fiber morphology, and congo red binding to assess fiber assembly kinetics.” As written these are inherent properties of the peptide as claimed. Electron microscopy is a means of measurement, but the claim does not distinguish what formation is required when viewed by EM. This is an investigatory technique and does not lead the artisan to a choosing of any particular structure that is within the claim limitations. Similarly, one can assess whether a peptide binds congo red via staining. However, this does not lead to any assessment of fiber assembly kinetics as recited. Similarly,

with respect to claim 131 circular dichroism at 208 and 220 nm is a means of assessment, but it does not specify the structure that the molecule of the claims must possess at that measurement. With respect to claim 134, the aggregates or 'ordered' but not "higher-ordered." The specification does not clarify that which is an ordered aggregate in comparison. Further to a "polymer" or "fiber morphology" these structural and functional recitations are also not clarified.

Applicants further argue that the standard assessment of "biological activity" should not be used to instant claims because evidence suggests the coalescing properties of SCHAG proteins are more permissive of sequence variation. Yet the specification does not clarify the coalescing properties. The agglomerations are not descriptively defined such that the artisan can assess their presence, or provide for suitable conditions for any sequence to obtain their presence. Applicants again refer to the specification at p. 4, 7-9, 51 and 61. However, the structural constraints of the claims are not directed to for example K, R, E, or D content for example. With reference to Exhibit C, the specification does not clarify the requirements for "SHAG" properties, define what the properties are or a means for obtaining them. The structure referred to in Exhibit is not an element of the claims. In addition the PQGGYQQYN is also not a limitation of the claims. Applicant's comments in subparagraph D are also noted. However, the references and arguments do not clarify the required third dimensional structure or the relationship between any sequence and particular third dimensional properties. The references are also post filing date references and cannot be relied on to describe Applicant's claims. In contrast to Applicant's assertion in subparagraph E

that the documents cited by the PTO support patentability, the documents evidence that the elements of the claims are not sufficiently described. The references recognize that structural alterations change secondary and tertiary structure, binding, aggregation, agglomeration, the ability to form beta pleated sheet structure or prion formation. The specification cannot refer to any means of experimental design to determine a formation as a description of all peptides that will or will not form a prion like structure under any and every testable condition. What is required of the specification is that it describes the peptides that do form a particular structure, describes the structure such that the artisan can immediately recognize it and a description of the conditions under which a particular sequence may be caused to do so. These requirements are not approached except for a few working embodiments that are not sufficiently descriptive of the claimed genus of all peptides capable of under some undisclosed conditions capable of forming some undefined structure. Accordingly, rejection is maintained.

12. Claims 121-135, 137-140, 144-145, 150-155, and 157-161 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aggregation as analyzed via spectroscopy and EM as exemplified throughout pp. 44-92 of the specification, see in particular experimentation with Sup35/URE2, does not reasonably provide enablement for the formation of fibrous polymers or for the scope of the polypeptides and fragments encompassed as directed to substituted amino acids and fragments of substituted amino acids such that they self-coalesce to form "fibrous polymers" or higher ordered aggregates". The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Applicants claims are directed to peptides and partial peptides with greater than single amino acid substitutions and which have the property of self-coalescing to form higher ordered aggregates or fibrous polymers. However, the specification does not teach the experimental variables amongst different experimental conditions and amino acid sequences that determine higher ordered aggregate structure or formation of fibrous polymer formation.

The specification does not enable the broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite structure is maintained. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular form and the skilled artisan would not expect similar structure amongst different sequences or different experimental conditions. For example, the artisan recognizes that protein aggregation is dependent upon multiple conditions inclusive of the amino acid sequence of the peptides, pH, temperature, salt concentration, the presence of alternative

peptides, cell membranes and other components that are of nearly unlimited breadth.

Such is extensively exemplified throughout the IDS. For example, IDS C12 Dagkesamanskaia teaches differential effect of fusion of glutathione S-transferase on aggregation of yeast Sup35 protein. IDS C15 DePace notes critical roles for amino-terminal Glutamine/Asparagine repeats in yeast prion aggregation. IDS C56 Glover notes the ability of various Hsp proteins to abrogate aggregation. IDS C64 Jackson notes various conditions (oxidation/reduction etc) which affect prion (aggregate) formation. Secondary structure is dependent and variable upon such factors.

Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. Further as to the terms "self-coalesce", "higher ordered aggregates" and "fibrous polymers" the skilled artisan is not provided with a recognized structural conformation or suitable conditions whereby any amino acid construct or composition may be assessed for assembly as required.

The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed polypeptides and fibrous polymers without further undue experimentation.

In the 12-5-05 response Applicants have addressed the concerns as noted in the

response to the written description rejection. These arguments have been fully considered but are not persuasive for the same reasons as maintained above. A teaching of a single experimental condition for a single peptide does not approach enabling all conditions under which all proteins form suitable nanotechnology products of particular form. As noted, agglomerations are dependent upon amino acid sequence in addition to experimental conditions. The product claims to the extent that they recite higher order structure and assert use in nanotechnology related applications is required to provide more than a simple description of an amino acid sequence as the claims are in part directed to secondary and tertiary structure which is not dependent upon amino acid sequence alone. Further the standard of an enabling structure is not that of the ability to make and to test. This experimentation is undue where there is not a predictable outcome. The scope of the claims is inclusive of nearly any amino acid sequence under any condition. Yet the specification has not provided enablement to the artisan such that any peptide amino acid structure may be converted to a prion or to prion-like structure. The Examiner does recognize that variability in Sup35 sequence may be provided without altering the ability to form prion-like molecules. However, the scope of the claims is beyond this in both structure and function and there is no correlating teaching that provides information as to how much variation under any particular conditions are tolerable without losing the ability to form such prion-like structures. Accordingly, undue experimentation on the artisan is required in the form of trial and error experimentation.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 126, 132-133, 150-155, 157-161 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 126 recites the limitation "the substituted amino acid" in reference to claims 124. There is insufficient antecedent basis or this limitation in the claim.

The breadth of claims 132-133 are indefinite as the claims refer to identity "except for said amino acid with the reactable side chain". These claims depend from claims 124 and 127 which stipulates 90% identity to 2-113 or 2-253 respectively with an amino acid with a reactable side chain as denoted in the claims. It is unclear if Applicants are referring to a peptide deleted or substituted at this residue or if Applicants are merely referring to a particular amino acids with a reactable side chain selected from the listed group. Clarification is required so that the scope of the claims may be properly interpreted.

The breadth of claims 150-155, 157-161 are indefinite as the structural limitations of elements (e) and (f) cannot be determined. The Examiner notes that the claims encompass partial fragments. The claims are also recited in comprising terms. Accordingly, the scope of these limitations with respect to the amino acids encompassed and/or required cannot be determined. However, the broadest reasonable interpretation is deemed to be inclusive of segments of two amino acids or a single amino acid residue as suitably encompassed by the recitation "an amino acid sequence" and further the recitation of "fragments".

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

16. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al., J. of Biol. Chem., 273(19):11806-814, 1998 as evidenced by Levy et al., J. Exp. Med., 169:1771-78, May 1989.

The claims are inclusively directed to polypeptide fragments that comprise substitutions of cysteine, lysine, tyrosine, glutamic acid, aspartic acid and arginine and that self-coalesce to form higher ordered aggregates. Cystatin C aggregates are suitable to form higher ordered aggregates that comprise fibrous polymers or fibrils in patients with HCHWA-I, see in particular Abstract and col. 1-2, p. 11806. The amino acid sequence of Cystatin C is evidenced by Levy et al., 1989. The polypeptides of the

claims relate to single amino acid substitutions. Any of the residues of Cystatin C either in the variant or wild type form that are of cysteine, lysine, tyrosine, glutamic acid, aspartic acid or arginine are sufficient to qualify as polypeptides comprising suitable portions or fragments that form higher ordered aggregate and fibrous polymer structures as the peptides are noted to form amyloid fibrils. All residues are exposed to the environment. Thus, Wei as evidenced by Levy fairly teach the invention.

In the response of 12-5-05 Applicants argue that Wie relates to a completely different protein that SEQ ID NO:2. However, SEQ ID NO:2 is not a requirement of the claims. In particular only a fragment is required and the fragment includes a cysteine in the context of a fragment of SEQ ID NO:2 and accordingly meets the structural constraints of the claims. In addition, as to higher order structure, fibril, polymers, coalescing etc., cystatin c was the amyloid peptide plaque formation found in these patients. Thus, the peptide provides for the amyloid like beta sheet preferred structure of the invention, see in particular pp. 1771-72 and thus the structure is evidenced. A single amino acid is comprised in the subject polypeptide of the claims. In addition, either wild-type or mutated cystatin is noted to form fibrous aggregate polymers. Accordingly rejection is maintained.

17. Claims 121-122, 139 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Kushnirov et al., Yeast, 6:461-472, 1990 IDS C76.

The claims are inclusively directed to polypeptide fragments that comprise substitutions of cysteine, lysine, tyrosine, glutamic acid, aspartic acid and arginine and that self-coalesce to form higher ordered aggregates. The claims also refer to peptides

of SEQ ID NO:2 with substitution at residue 184. Residue 184 is K, lysine, and is in the context of the amino acid sequence “TKE”. Kushnirov teach both divergence and conservation of SUP2 (SUP35) gene of yeast *Pichia pinus* and *Saccharomyces cerevisiae*. Mutation of the lysine residue to glutamate/glutamic acid results in the sequence “TEE” found in *Pichia pinus* SUP2/SUP35 at residues 215-217. The *Pichia* variant thus comprises a suitable substitution fragment where the substitution is glutamate/glutamic acid. All residues are exposed to the environment. Kushnirov is silent as to the aggregating properties. However, it is noted that the peptide is significantly homologous (60.6%) to the *cerevisiae* protein. A peptide and its properties cannot be separated. To the extent that the structural constraints of the peptides are fairly met, the properties of forming higher ordered aggregates and fibrous polymers are deemed inherent absent convincing factual evidence to the contrary. The PTO has insufficient resources to test the Kushnirov peptide for its aggregating properties. Thus the reference teachings anticipate the claimed invention.

In the 12-5-05 response Applicants argue that Kushnirov does not anticipate as claim 144 is amended to cysteine. This argument has been fully considered but is not persuasive as the claim remains drawn to glutamate. Rejection over claim 123 is obviated via amendment to cysteine.

Further to newly presented claims 150-151 and 157-158 the preamble of the claim recites a polypeptide that comprises “an amino acid sequence”. This recitation of “an” is inclusive of any and accordingly these claims are also rejected for the reasons noted above. All amino acids have affinity for specific amino acid specific antibody. All

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amino acids are also light altering substituents as they may be measured via light spectroscopy.

RESULT 2

S12921

suppressor 2 protein - yeast (Pichia pinus)

N;Alternate names: SUP2 protein

C;Species: Pichia pinus

C;Date: 16-Sep-1992 #sequence_revision 16-Sep-1992 #text_change 09-Jul-2004

C;Accession: S12921

R;Kushnirov, V.V.; Ter-Avanesyan, M.D.; Didichenko, S.A.; Smirnov, V.N.; Chernoff, Y.O.; Derkach, I.L.; Novikova, O.N.; Ingesson, S.G.; Neistat, M.A.; Tolstorukov, I.I.

Yeast 6, 461-472, 1990

A;Title: Divergence and conservation of SUP2(SUP35) gene of yeasts Pichia pinus and Saccharomyces cerevisiae.

A;Reference number: S12921; MUID:91181341; PMID:2080663

A;Accession: S12921

A;Molecule type: DNA

A;Residues: 1-741

A;Cross-references: UNIPROT:P23637; UNIPARC:UPI0000035CFC; EMBL:X56910; NID:g3235; PIDN:CAA40231.1; PID:g3236

C;Genetics:

A;Gene: SUP2

C;Superfamily: suppressor 2 protein; translation elongation factor Tu homology

C;Keywords: GTP binding; nucleotide binding; P-loop; phosphoprotein

F;319-467/Domain: translation elongation factor Tu homology

F;325-332/Region: nucleotide-binding motif A (P-loop)

F;464-467/Region: GTP-binding NKXD motif

F;331/Binding site: GTP (Lys) #status predicted

Query Match 60.6%; Score 2175; DB 2; Length 741;

Best Local Similarity 60.9%; Pred. No. 1.6e-107;

Matches 433; Conservative 86; Mismatches 128; Indels 64; Gaps 15;

Qy 11 QNYQQYSQNGNQQQGNRYQGYQAYNAQAQPAGGYYQNYQGYSGYQQGGYQQYNPDAGYQ 70
| ||:|| ||:|| ||:|| ||:|| ||:|| || |

Db 56 QQEQQFGQYQQQQQNYNQ-GGYNYYNNR---GGYSNNRGGYNNNSNRGGYSYN--SYN 107

Qy 71 QQYNPQGGYQQYNPQGGYQQQFNPGGRGNYKNFNYNNN--LQGYQAGF----QPQSQ 122
| |||| || |||:|| ||:|| || |

Db 108 TNSN-QGGYSYN-----NNYANNSYNNNNNNNNQGYNNYNSQPQQ 151

Qy 123 G-----MSLNDFQKQQKQAA---PKPKKTLKL-VSSSGIKLANATKKVGTKPAES 168
|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||:|||: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Db 152 DQQQETGSGQMSLEDYQKQQKESLNKLNTPKKVLKLNLNSSTVKAPIVKKKEEEPVNQ 211

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Qy 169 DKKEEEKSAE--TKEPTXEPTKVEE-----PVKKEEKPVQTEEKTEEKS--EL 212
:||:|| :|| |||| ||:|| || |||| :||
Db 212 ESKTEEPAKEEIKNQEPAEAENKVEEESKVEAPTAAKPVSESEFPAST-PKTEAKASKEV 270

Qy 213 PKVEDLKISESTHNTNNANVTSADALIKEQEEEVDEVVNDMFGGKDHVSLIFMGHVDAG 272
| : :||:||:||:|| :||:||:||:||:||:||
Db 271 AAAAAALKKEVSQLAKESNVTNADALVKEQEEQIDASIVNDMFGGKDHMSIIFMGHVDAG 330

Qy 273 KSTMGGNLLYLTGSVDKRTIEKYEREAKDAGRQGWYLSWVMDTNKEERNDGKTIEVGKAY 332
||||:||:||:||:||:||:||:||:||:||:||:||
Db 331 KSTMGGNLLFTGAVDKRTVEKYEREAKDAGRQGWYLSWVMDTNKEERNDGKTIEVGKSY 390

Qy 333 FETEKRRYTILDAPGHKMYVSEIMGGASQADGVVLVISARKGEYETGFERGGQTREHALL 392
||:||:||:||:||:||:||:||:||:||:||:||
Db 391 FETDKRRYTILDAPGHKLYISEMIGGASQADGVVLVISSRKGEYEAGFERGGQSREHAIL 450

Qy 393 AKTQGVNKMVVVNVKMDDPVNWSKERYDQCNSVSNFLRAIGYNIKTDVVFMPVSGYSG 452
||||:||:||:||:||:||:||:||:||:||:||
Db 451 AKTQGVNKLVVVINKMDPTVNWSKERYEECTTKLAMYLKGVGYQ-KGDVLFMPVSGYTG 509

Qy 453 ANLKDHDVDPKECPWYTGPTLLEYLDTMNHVDRHINAPFMLPIAAKMKDLGTIVEGKIESG 512
| ||:||:||:||:||:||:||:||:||:||:||
Db 510 AGLKERSQKDAPWYNGPSLLEYLDSMPLAVRKINDPFMLPISSKMKDLGTIEGKIESG 569

Qy 513 HIKKGQSTLLMPNKTAVEIQNIYNETENEVDMAMCGEQVKLRIKGVEEEDISPGFVLTSP 572
||:||:||:||:||:||:||:||:||:||:||:||
Db 570 HVKKGQNLLVMPNKTQEVTTIYNETEAEADSAFCGEQVRLRLRGIEEEDLSAGYVLSSI 629

Qy 573 KNPIKSVTKFVAQIAIVELKSIIAGFSCVMHVHTAIEEVHIVKLLHKEKGTRKSKKP 632
:||:||:||:||:||:||:||:||:||:||
Db 630 NHPVKTVTRFEAQIAIVELKSILSTGFSCVMHVHTAIEEVFTQLLHNLQKGTNRRSKKA 689

Qy 633 PAFAKKGMKVIAVLETEAPVCVETYQDYPQLGRFTLRDQGTTIAIGKIVKI 683
||:||:||:||:||:||:||:||:||:||:||
Db 690 PAFAKQGMKIIAVLETTEPVCIESYDDYPQLGRFTLRDQGQTIAIGKVTKL 740

18. Claims 144-145, 139-140, 150-155, and 157-161 are rejected under 35 U.S.C. 102(e) as being anticipated by Pruisner et al., US 6,277,970, filed 5-11-99 and issued 8-21-01.

Claims 144-145 are drawn to peptides comprising a SCHAG amino acid fragment of SEQ ID NO:2 that self coalesces to form higher ordered aggregates. Claim 150 is also directed to SCHAG fragments as encompassed by the preamble recitation of "an amino acid sequence," regardless of self coalescing activity as well as fragments that self coalesce as encompassed by element "c". Pruisner et al teach prion like peptides termed Doppel or Dpl that aggregate and self coalesce into higher ordered structures such as prion proteins. Residue #2 of SEQ ID NO:2 is in the context of amino acids "MSD". Mutation of residue #2 to cysteine as preferred results in fragments comprised of residues "CD" or cys-asp. Residue #184 of SEQ ID NO:2 is in the context of "TKE". Mutation of residue #184 to cysteine as preferred results in fragments comprised of residues "CE" or cys-glu. Pruisner's peptides comprise these fragments, see in particular SEQ ID NO :2 and 4 of Pruisner appended below. The peptides are further disclosed for use in screening assays and when used in such the peptides are noted to be modified so as to include suitable labels such as enzymes, fluorescent molecules or specific binding partners as preferred and may further be attached to a solid support for assay. In addition, the assay may be conducted via multiple label(s) as indicated via plurality and/or a combination of labels as in a double label employing one or more options of different labels. Accordingly, the reference teachings anticipate the claimed invention.

Detailed Description Text (115):

The screening assay can be a binding assay, wherein one or more of the molecules may be joined to a label, and the label directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, enzymes, specific binding molecules, particles, e.g. magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and

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antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

Detailed Description Text (139):

The insoluble supports may be any compositions to which polypeptides can be bound, which is readily separated from soluble material, and which is otherwise compatible with the overall method. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports to which the receptor is bound include beads, e.g. magnetic beads, membranes and microtiter plates. These are typically made of glass, plastic (e.g. polystyrene), polysaccharides, nylon or nitrocellulose. Microtiter plates are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples.

<210> SEQ ID NO 2

<211> LENGTH: 176

<212> TYPE: PRT

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 2

Met Arg Lys His Leu Ser Trp Trp Trp Leu Ala Thr Val Cys Met Leu
Leu Phe Ser His Leu Ser Ala Val Gln Thr Arg Gly Ile Lys His Arg
Ile Lys Trp Asn Arg Lys Ala Leu Pro Ser Thr Ala Gln Ile Thr Glu
Ala Gln Val Ala Glu Asn Arg Pro Gly Ala Phe Ile Lys Gln Gly Arg
Lys Leu Asp Ile Asp Phe Gly Ala Glu Gly Asn Arg Tyr Tyr Glu Ala
Asn Tyr Trp Gln Phe Pro Asp Gly Ile His Tyr Asn Gly Cys Ser Glu
Ala Asn Val Thr Lys Glu Ala Phe Val Thr Gly Cys Ile Asn Ala Thr
Gln Ala Ala Asn Gln Gly Glu Phe Gln Lys Pro Asp Asn Lys Leu His
Gln Gln Val Leu Trp Arg Leu Val Gln Glu Leu Cys Ser Leu Lys His
Cys Glu Phe Trp Leu Glu Arg Gly Ala Gly Leu Arg Val Thr Met His
Gln Pro Val Leu Leu Cys Leu Leu Ala Leu Ile Trp Leu Met Val Lys

<210> SEQ ID NO 4

<211> LENGTH: 179

<212> TYPE: PRT

<213> ORGANISM: rat *rattus*

<400> SEQUENCE: 4

Met Lys Asn Arg Leu Gly Thr Trp Gly Leu Ala Ile Leu Cys Leu Leu
Leu Ala Ser His Leu Ser Thr Val Lys Ala Arg Gly Ile Lys His Arg

Phe Lys Trp Asn Arg Lys Val Leu Pro Ser Ser Gly Gln Ile Thr Glu
Ala Gln Val Ala Glu Asn Arg Pro Gly Ala Phe Ile Lys Gln Gly Arg
Lys Leu Asp Ile Asp Phe Gly Ala Glu Gly Asn Lys Tyr Tyr Ala Ala
Asn Tyr Trp Gln Phe Pro Asp Gly Ile Tyr Tyr Glu Gly Cys Ser Glu
Ala Asn Val Thr Lys Glu Val Leu Val Thr Arg Cys Val Asn Ala Thr
Gln Ala Ala Asn Gln Ala Glu Phe Ser Arg Glu Lys Gln Asp Ser Lys
Leu His Gln Arg Val Leu Trp Arg Leu Ile Lys Glu Ile Cys Ser Thr
Lys His Cys Asp Phe Trp Leu Glu Arg Gly Ala Ala Leu Arg Ile Thr
Val Asp Gly Leu Gln Ala Met Val Cys Leu Leu Gly Phe Ile Trp Phe
Ile Val Lys

19. Claims 121-123, 139-140, 144-145, 150-155, 157-161 are rejected under 35 U.S.C. 102(e) as being anticipated by Glabe et al., US 6,600,017 filed 8-13-1998 and issued 7-29-03.

Claims 144-145 are drawn to peptides comprising a SCHAG amino acid fragment of SEQ ID NO:2 that self coalesces to form higher ordered aggregates. Claim 150 is also directed to SCHAG fragments as encompassed by the preamble recitation of "an amino acid sequence," regardless of self coalescing activity as well as fragments that self coalesce as encompassed by element "c". Glabe et al teach beta amyloid peptides that form beta-pleated sheet aggregates and form fibrils. The beta amyloid peptides are substituted at one or more residues with fluorescently labeled cysteine. Residue #2 of SEQ ID NO:2 as claimed is in the context of amino acids "MSD". Mutation of residue #2 to cysteine as preferred results in fragments comprised of residues "MC" or "CD". Residue #184 of SEQ ID NO:2 as claimed is in the context of "TKE". Mutation of residue #184 to cysteine as preferred results in fragments comprised of residues "CE". Cysteine amino acid substitution as taught by Glabe

particularly at residue 2, 6, 10, 21, 22 or 36 results in the proper context of a fragment comprising one of "MC", "CD", or "CE". These fragments are in the context of the larger beta-amyloid peptides that are additionally noted to aggregate as in wild type. The reference further notes where more than a single cysteine substitution and/or label may be provided. The peptides are further disclosed for use in screening assays and when used in such the peptides are noted to be provided or tested for binding on solid supports. Accordingly, the reference teachings anticipate the claimed invention. The following excerpts from the patent are particularly noted.

In general, the invention features a composition that includes an aggregating amyloid A. β . peptide to which is covalently bonded a fluorescent label. In one preferred embodiment, the fluorescent label is covalently bonded to a cysteine amino acid. The invention also features a method for generating such a preferred aggregating amyloid A. β . peptide. The method involves (a) generating an amyloid A. β . peptide including a cysteine amino acid substitution; (b) covalently bonding a fluorescent label to the peptide at the cysteine amino acid; and (c) determining whether the peptide is capable of aggregating with another A. β . peptide.

The aggregating A. β . peptides of the invention also find use in screens for identifying compounds capable of affecting the aggregation of A. β . amyloid peptide. One particular method involves (a) providing a sample of A. β . amyloid peptide; (b) contacting the sample with (i) an aggregating amyloid A. β . peptide to which is covalently bonded a fluorescent label; and (ii) a candidate compound; and (c) measuring association of the fluorescent label with the sample, a change in the level of fluorescent label found in association with the sample relative to a control sample lacking the candidate compound being an indication that the compound is capable of affecting A. β . amyloid peptide aggregation. In a preferred embodiment of this method, the sample includes unlabeled A. β . amyloid peptide bound to a solid support, and the aggregation is measured by association of the fluorescent label with the solid support.

The aggregation properties of the fluorescent derivatives were compared to wild type A. β . under physiological conditions (e.g., Tris buffered saline at pH 7.4) where the peptide was largely soluble, as well as under conditions that were known to promote fibril assembly (e.g., pH 5.0 and pH 7.4 in the presence of Zn.⁺⁺) (FIG. 1). As shown in FIG. 1, at pH 7.4 and at pH 5.0, all of the fluorescent peptides were indistinguishable from wild type A. β .. In the presence of 70 μ M Zn.⁺⁺, the fluorescein and AEDANS labeled A. β . peptides aggregated to approximately 50-75% of the extent of wild type A. β .. However trp substitution at residue 10 did not alter the aggregation behavior in response to Zn.⁺⁺. The oligomeric structure of the fluorescent peptides was characterized by gel filtration, and the fluorescent peptides were found to elute at the same position as wild type A. β . (FIGS. 2A and 2B). The elution position corresponded to an apparent molecular mass of 9,000 Da established by the elution behavior of a series of calibration standards (FIG. 2A, inset). The calibration curve also indicated that the expected elution position for a peptide of the mass of monomeric A. β . was well separated from the observed elution position of A. β .. Nanomolar concentrations of μ g.14 C-labeled A. β .1-40 also eluted at the position expected for a dimer (FIG. 2B).

In addition to the A. β . peptides described above, an extended A. β . peptide was generated having the following sequence: DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIA (SEQ ID NO: 2). This peptide was chemically synthesized and fluorescently labeled (as described above) at the amino acid positions described above. These fluorescent derivatives were found to form fibrils, to aggregate, and to bind cells in a manner analogous to the unlabeled wild type peptide.

Other fluorescently labeled A. β . peptides possessing the aggregation properties of wild-type A. β . may be synthesized and tested using the techniques described above. In particular, other cysteine-substituted peptides may be made, fluorescently labeled, and tested for aggregation properties (for example, by centrifugation, gel filtration, or FRET analysis). In preferred examples, using the methodologies described herein, A. β . peptides may be cysteine-substituted and fluorescently labeled at any hydrophobic amino acid position. Alternatively, A. β . peptides may be labeled at the free amino group. In addition, A. β . peptides may be produced which have multiple sites labeled, if desired, with different fluorescent tags. Again, aggregation activity is tested, for example, as described herein.

A. β . fragments having cysteine substitutions (for example, those substitutions described above) may also be synthesized, fluorescently labeled, and tested for activity. One preferred A. β . fragment includes amino acids 10-25 of SEQ ID NO: 1.

In addition, any other appropriate fluorescent label may be utilized for peptide synthesis and the methods of the invention. Preferred fluorescent labels include, without limitation, any fluorescent label having a thiol-reactive group. Such fluorescent labels include, for example, thiol-reactive BODIPY, fluorescein, Oregon Green, tetramethylrhodamine, eosin, erythrosin, coumarin, pyridyloxazole, benzoxadiazole, aminonaphthalene, pyrene, maleimide, a lanthanide cryptate, a lanthanide chelate, and Texas Red derivatives (commercially available, for example, from Molecular Probes, Eugene, Oreg.).

In addition to diagnostic utilities, the fluorescent peptides described herein are also useful as reagents for screening assays for the identification of compounds that modulate A. β . aggregation. Typically, such screening assays are carried out for the purpose of isolating or identifying compounds that inhibit A. β . aggregation, but may also be used to identify compounds that enhance aggregation.

20. Claims 145, 139, 150-152, and 154 are rejected under 35 U.S.C. 102(e) as being anticipated by Pruisner et al., 5,962,669 issued 10-5-1999.

Claims 144-145 are drawn to peptides comprising a SCHAG amino acid fragment of SEQ ID NO:2 that self coalesces to form higher ordered aggregates. Claim 150 is also directed to SCHAG fragments as encompassed by the preamble recitation of "an amino acid sequence," regardless of self coalescing activity as as well as fragments that self coalesce as encompassed by element "c". The Pruisner et al.,

reference teaches prion molecule proteins and PPMF that facilitate formation of prion fibrils. The PPMF is a rate-limiting step and the molecules bind prion peptides in the non-scrapie form. Once the peptides are converted PPMF no longer binds. While bound, PPMF is a suitable substituent that has specific affinity as a binding partner. It is also a catalyst to Scrapie formation. As noted above, residue #2 of SEQ ID NO:2 as claimed is in the context of amino acids "MSD". Mutation of residue #2 to cysteine as preferred results in fragments comprised of residues "MC". The Pruisner peptides comprise residues "MC". These fragments are in the context of the larger Prion molecules and complex as in scrapie and non-scrapie prion molecule formations with Prp and PPMF. The binding sites are as particularly noted throughout the figures 6, 7, 10, 11 and 14 noting particular mutation sites. Accordingly, the reference teachings anticipate the claimed invention. The following excerpts from the patent are particularly noted.

A protein designated Prion Protein Modulator Factor (PPMF) is disclosed which protein is an auxiliary factor in prion replication. PPMF is primarily characterized by its ability to bind to PrP.sup.C and facilitate a conformational change from PrP.sup.C to PrP.sup.Sc. A discontinuous epitope on PrP.sup.C comprising residues 172, 215 and 219 of human PrP.sup.C binds PPMF which is encoded by a nucleotide sequence derived from an organism selected from the group consisting of cow, sheep, mouse, hamster and human. In converting PrP.sup.C to PrP.sup.Sc the PPMF forms a PrP.sup.C /PrP.sup.Sc complex and is a rate limiting compound in the formation of that complex. Molecules, including antibodies, which bind PPMF or its epitope on PrP.sup.C are useful in the treatment of prion disease. Pharmacophores of the PrP.sup.C epitope are disclosed as are useful therapeutics and pharmacophores of the PPMF surface which binds PrP.sup.C. Animals resistant to prion disease are taught as are genes for producing such animals. Assay systems are disclosed which use PPMF to amplify PrP.sup.Sc is a sample being tested.

In order for a mammal to develop a prion disease, PrP.sup.C must be converted to PrP.sup.Sc, i.e., prions must be formed. In order for prions to be formed, three compounds must be present which are PrP.sup.C, PrP.sup.Sc, and PPMF. Because PPMF is a rate-limiting compound in the formation of prions, (if not recycled) an animal which is infected with prions (i.e. PrP.sup.Sc) may develop symptoms of prion disease very slowly. This is not desirable when the animal is being used as a test animal in order to determine if the prions are present within a sample. Thus, the administration of PPMF to such test animals can greatly reduce the amount of time necessary for the formation of prions and thereby reduce the amount of time necessary to pass before the observation of the first symptoms of prion disease.

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(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

#acids (A) LENGTH: 254 amino
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: peptide
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: MOUSE PRI - #ON PROTEIN, MoPrP
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
 - Met Ala Asn Leu Gly Tyr Trp Leu Leu Ala Le - #u Phe Val Thr Met Trp
 - Thr Asp Val Gly Leu Cys Lys Lys Arg Pro Ly - #s Pro Gly Gly Trp Asn
 - Thr Gly Gly Ser Arg Tyr Pro Gly Gln Gly Se - #r Pro Gly Gly Asn Arg
 - Tyr Pro Pro Gln Gly Gly Thr Trp Gly Gln Pr - #o His Gly Gly Trp
 - # 60
 - Gly Gln Pro His Gly Gly Ser Trp Gly Gln Pr - #o His Gly Gly Ser Trp
 - #80
 - Gly Gln Pro His Gly Gly Trp Gly Gln Gl - #y Gly Gly Thr His Asn
 - # 95
 - Gln Trp Asn Lys Pro Ser Lys Pro Lys Thr As - #n Leu Lys His Val Ala
 - # 110
 - Gly Ala Ala Ala Ala Gly Ala Val Val Gly Gl - #y Leu Gly Gly Tyr Met
 - # 125
 - Leu Gly Ser Ala Met Ser Arg Pro Met Ile Hi - #s Phe Gly Asn Asp Trp
 - # 140
 - Glu Asp Arg Tyr Tyr Arg Glu Asn Met Tyr Ar - #g Tyr Pro Asn Gln Val
 - 145 1 - #50 1 - #55 1 -
 - #60
 - Tyr Tyr Arg Pro Val Asp Gln Tyr Ser Asn Gl - #n Asn Asn Phe Val His
 - # 175
 - Asp Cys Val Asn Ile Thr Ile Lys Gln His Th - #r Val Thr Thr Thr
 - # 190
 - Lys Gly Glu Asn Phe Thr Glu Thr Asp Val Ly - #s Met Met Glu Arg Val
 - # 205
 - Val Glu Gln Met Cys Val Thr Gln Tyr Gln Ly - #s Glu Ser Gln Ala Tyr
 - # 220
 - Tyr Asp Gly Arg Arg Ser Ser Ser Thr Val Le - #u Phe Ser Ser Pro Pro
 - 225 2 - #30 2 - #35 2 -
 - #40
 - Val Ile Leu Leu Ile Ser Phe Leu Ile Phe Le - #u Ile Val Gly
 - # 250

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15
 - Ser Asp Leu Gly Leu Cys Lys Lys Arg Pro Ly - #s Pro Gly Gly Trp Asn
 # 30
 - Thr Gly Gly Ser Arg Tyr Pro Gly Gln Gly Se - #r Pro Gly Gly Asn Arg
 # 45
 - Tyr Pro Pro Gln Gly Gly Trp Gly Gl - #n Pro His Gly Gly Gly
 # 60
 - Trp Gly Gln Pro His Gly Gly Trp Gly Gl - #n Pro His Gly Gly Gly
 #80
 - Trp Gly Gln Pro His Gly Gly Trp Gly Gl - #n Gly Gly Thr His

95
 - Ser Gln Trp Asn Lys Pro Ser Lys Pro Lys Th - #r Asn Met Lys His Met
 # 110
 - Ala Gly Ala Ala Ala Ala Gly Ala Val Val Gl - #y Gly Leu Gly Gly Tyr
 # 125
 - Met Leu Gly Ser Ala Met Ser Arg Pro Ile II - #e His Phe Gly Ser Asp
 # 140
 - Tyr Glu Asp Arg Tyr Tyr Arg Glu Asn Met Hi - #s Arg Tyr Pro Asn Gln
 145 1 - #50 1 - #55 1 -
 #60
 - Val Tyr Tyr Arg Pro Met Asp Glu Tyr Ser As - #n Gln Asn Asn Phe Val
 # 175
 - His Asp Cys Val Asn Ile Thr Ile Lys Gln Hi - #s Thr Val Thr Thr Thr
 # 190
 - Thr Lys Gly Glu Asn Phe Thr Glu Thr Asp Va - #l Lys Met Met Glu Arg
 # 205
 - Val Val Glu Gln Met Cys Ile Thr Gln Tyr Gl - #u Arg Glu Ser Gln Ala
 # 220
 - Tyr Tyr Gln Arg Gly Ser Ser Met Val Leu Ph - #e Ser Ser Pro Pro Val
 225 2 - #30 2 - #35 2 -
 #40
 - Ile Leu Leu Ile Ser Phe Leu Ile Phe Leu II - #e Val Gly
 # 250
 - (2) INFORMATION FOR SEQ ID NO:23:
 - (i) SEQUENCE CHARACTERISTICS:
 #acids (A) LENGTH: 263 amino
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: peptide
 - (vi) ORIGINAL SOURCE:
 (A) ORGANISM: BOVINE PR - #ION PROTEIN, BoPrP
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:
 - Met Val Lys Ser His Ile Gly Ser Trp Ile Le - #u Val Leu Phe Val Ala
 # 15
 - Met Trp Ser Asp Val Gly Leu Cys Lys Lys Ar - #g Pro Lys Pro Gly Gly
 # 30
 - Trp Asn Thr Gly Gly Ser Arg Tyr Pro Gly Gl - #n Gly Ser Pro Gly Gly
 # 45
 - Asn Arg Tyr Pro Pro Gln Gly Gly Tr - #p Gly Gln Pro His Gly

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60
- Gly Gly Trp Gly Gln Pro His Gly Gly Gly Tr - #p Gly Gln Pro His Gly
#80
- Gly Gly Trp Gly Gln Pro His Gly Gly Gly Tr - #p Gly Gln Pro His Gly
95
- Gly Gly Gly Trp Gly Gln Gly Gly Thr His Gl - #y Gln Trp Asn Lys Pro
110
- Ser Lys Pro Lys Thr Asn Met Lys His Val Al - #a Gly Ala Ala Ala Ala
125
- Gly Ala Val Val Gly Gly Leu Gly Gly Tyr Me - #t Leu Gly Ser Ala Met
140
- Ser Arg Pro Leu Ile His Phe Gly Ser Asp Ty - #r Glu Asp Arg Tyr Tyr
145 1 - #50 1 - #55 1 -
#60
- Arg Glu Asn Met His Arg Tyr Pro Asn Gln Va - #l Tyr Tyr Arg Pro Val
175
- Asp Gln Tyr Ser Asn Gln Asn Asn Phe Val Hi - #s Asp Cys Val Asn Ile
190
- Thr Val Lys Glu His Thr Val Thr Thr Th - #r Lys Gly Glu Asn Phe
205
- Thr Glu Thr Asp Ile Lys Met Met Glu Arg Va - #l Val Glu Gln Met Cys
220
- Val Thr Gln Tyr Gln Lys Glu Ser Gln Ala Ty - #r Tyr Asp Gln Gly Ala
225 2 - #30 2 - #35 2 -
#40
- Ser Val Ile Leu Phe Ser Ser Pro Pro Val II - #e Leu Leu Ile Ser Phe
255
- Leu Ile Phe Leu Ile Val Gly
260
- (2) INFORMATION FOR SEQ ID NO:24:
- (i) SEQUENCE CHARACTERISTICS:
#acids (A) LENGTH: 255 amino
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (vi) ORIGINAL SOURCE:
 (A) ORGANISM: SHEEP PRI - #ON PROTEIN, ShPrP
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:
- Met Val Lys Ser His Ile Gly Ser Trp Ile Le - #u Val Leu Phe Val Ala
15
- Met Trp Ser Asp Val Gly Leu Cys Lys Lys Ar - #g Pro Lys Pro Gly Gly
30
- Trp Asn Thr Gly Gly Ser Arg Tyr Pro Gly Gl - #n Gly Ser Pro Gly Gly
45
- Asn Arg Tyr Pro Pro Gln Gly Gly Gly Tr - #p Gly Gln Pro His Gly
60
- Gly Gly Trp Gly Gln Pro His Gly Gly Gly Tr - #p Gly Gln Pro His Gly
#80
- Gly Ser Trp Gly Gln Pro His Gly Gly Gly Gl - #y Trp Gly Gln Gly Gly
95
- Ser His Ser Gln Trp Asn Lys Pro Ser Lys Pr - #o Lys Thr Asn Met Lys
110

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- His Val Ala Gly Ala Ala Ala Ala Gly Ala Va - #1 Val Gly Gly Leu Gly
125
- Gly Tyr Met Leu Gly Ser Ala Met Ser Arg Pr - #0 Leu Ile His Phe Gly
140
- Asn Asp Tyr Glu Asp Arg Tyr Tyr Arg Glu As - #n Met Tyr Arg Tyr Pro
145 1 - #50 1 - #55 1 -
#60
- Asn Gln Val Tyr Tyr Arg Pro Val Asp Gln Ty - #r Ser Asn Gln Asn Asn
175
- Phe Val His Asp Cys Val Asn Ile Thr Val Ly - #s Gln His Thr Val Thr
190
- Thr Thr Thr Lys Gly Glu Asn Phe Thr Glu Th - #r Asp Ile Lys Ile Met
205
- Glu Arg Val Val Glu Gln Met Cys Ile Thr Gl - #n Tyr Gln Arg Glu Ser
220
- Gln Ala Tyr Tyr Gln Arg Gly Ala Ser Val II - #e Leu Phe Ser Ser Pro
225 2 - #30 2 - #35 2 -
#40
- Pro Val Ile Leu Leu Ile Ser Phe Leu Ile Ph - #e Leu Ile Val Gly
255

Conclusion

21. No claims are allowed.
22. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from

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7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
June 21, 2006

Sharon L. Turner, Ph.D.
SHARON TURNER, PH.D.
PRIMARY EXAMINER

6-21-06